PATENT
0147-199P

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANTS:	KUFER, Peter et al.	Conf.:	3425
Appl. No.:	09/554,465	GROUP:	1641
FILED:	October, 19, 2000	EXAMINER:	CHEU, CHANGHWA J

FOR: A NOVEL METHOD FOR IDENTIFYING BINDING SITE DOMAINS THAT RETAIN THE CAPACITY OF BINDING TO AN EPITOPE

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

October 10, 2006

Sir:

I, Dr. Tobias Raum of the Research & Development department, Micromet AG, Germany, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am Director Lead Discovery/Human Antibody Technology/Immunotherapy.

I am familiar with the above referenced patent application, as well as the development, usages and properties of antibodies, epitope binding domains and recombinant polypeptides.

I would consider myself one of ordinary skill in the art of molecular biology, immunology and protein engineering as of November 1997.

I have read and understand the subject matter of the Office Action issued on April 24, 2006, and offer the following comments and references in support of the patentability of the present invention:

By the use of PCR gene synthesis and cloning techniques it was possible in 1997 for the person skilled in the art to graft defined CDRs of a first antibody molecule into a framework of a second antibody molecule and thereby retaining the original specificity and activity of the first antibody without the requirement of any further inventive input. A general method to obtain a binding molecule comprising the defined CDRs derived from a first antibody molecule in a framework of a second antibody molecule is extensively described e.g. in the US Patent 5,225,539. In this patent an invention is claimed which "relates to altered antibodies in which the complementarity determining regions (CDRs) in the light or heavy chain variable domains of the antibody have been replaced by the analogous CDRs from an antibody of different specificity"; column 1, line 8 to 12 of the '539 patent). In the specification the state of the art at the filing date of the application underlying the '539 patent is discussed as follows:

> "The variable domains of each pair of light and heavy chains form the antigen binding site. The domains on the light and heavy chains have the same general structure and each domain comprises four framework regions, whose sequences are relatively conserved, connected by three hypervariable or complementarity determining regions (CDRs) (see Kabat, E. A., Wu, T. T., Bilofsky, H., Reid-Miller, M. and Perry, H., in "Sequences of Proteins of Immunological Interest", US Dept. Health and Human Services 1983). The four framework regions largely adopt a β-sheet conformation and the CDRs form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs are held in close

proximity by the framework regions and with the CDRs from the other domain contribute to the formation of the antigen binding site.
For a more detailed account of the structure of variable domains, reference may be made to: Poljak, R. J., Amzel, L. M., Avey, H. P., Chen, B. L., Phizackerly, R. P. and Saul, F., PNAS USA, 70, 3305-3310, 1973; Segal, D. M., Padlan, E. A., Cohen, G. H., Rudikoff, S., Potter, M. and Davies, D. R., PNAS USA, 71, 4298-4302, 1974; and Marquart, M., Deisenhofer, J., Huber, R. and Palm, W., J. Mol. Biol., 141, 369-391, 1980." (see column 1, line 32 to 56 of the '539 patent)

The invention claimed in the '539 patent "provides an altered antibody in which at least parts of the CDRs in the light or heavy chain variable domains have been replaced by the analogous CDRs from an antibody of different specificity"; see column 3, line 28 to 32. It is further stated in the patent that"[a]lthough the CDRs may be derived from an antibody of the same class or even subclass as the antibody from which the framework regions are derived, it is envisaged that the CDRs will be derived from an antibody of different class and preferably from an antibody from a different species."; see column 3, line 39 to 44 of the '539 patent. The enablement of the method and the altered antibodies claimed in the '539 patent is demonstrated in the appended example 1; see columns 6 to 9 of the patent.

The determination of the amino acid sequence of the CDRs of a VL or a VH domain of a first antibody and, thus, the differentiation between CDRs and framework regions according to a Kabat was state of the art in 1991 according to the cited passages in the '539 patent. This identification of the CDRs according to Kabat was further described in a later version of the cited Kabat reference, i.e. in Kabat et al. (1991;

Sequences of Proteins of Immunological Interest, National Institutes of Health Publication 5th ed.). The 1991 5th edition of the Kabat reference, which is an update of the 4th edition to which was referred in the '539 patent, is cited in the patent application US 09/554,465. A copy of the relevant pages of the 1991 5th edition of the Kabat reference is enclosed.

In view of the presented state of the art in the year 1997, the CDRs within given human or mouse antibody V-regions can be determined by looking at the amino acid sequence of the V-regions and following the guidance derivable from the 1991 Kabat reference. In particular, the CDRs in a VH-sequence can be determined as follows:

The VH region has a typical cysteine at position 22 (Kabat position; in the present application '465 it is located at position 23 for cloning reasons). The first amino acid of CDR 1 always starts at position 9 after the cysteine (Kabat position 31). The CDR1 is typically of 5 to 7 amino acids in length and ends directly before a conserved motive like WVR (Trp, Val, Arg), WIR (Trp, Ile, Arg), or WVK (Trp, Val, Lys) (Kabat position of W (Trp): 36). FR2 (frame work region 2) has always a length of 14 amino acids and is followed by CDR 2. A typical motive of the last 4 amino acids of FR2 is EWIG (Glu, Trp, Ile, Gly), EWVA (Glu, Trp, Val, Ala) or EWVS (Glu, Trp, Val, Ser). The last amino acid of FR2 is at Kabat position 49. The length of CDR 2 normally varies between 16 and 19 amino acids. CDR 2 is followed by FR3 that has a length of 32 amino acids in almost every case. It starts typically with a motive as RVT (Arg, Val, Thr), RFT (Arg, Phe, Thr), RLT (Arg, Leu, Thr), RFA (Arg, Phe, Ala) or KAT (Lys, Ala, Thr) (first amino acid of FR3 is at Kabat position 66) and ends mostly with a CAR (Cys, Ala, Arg) motive (last

amino acid of FR3 is at Kabat position 94). The CDR 3 is very variable in length and often consists of 4 to more than 16 amino acids. It is followed by FR4 that most often starts with a W (Trp) (Kabat position 103), is most often followed by a GRG (Gly, Arg, Gly), GTG (Gly, Thr, Gly), GAG (Gly, Ala, Gly) or GQG (Gly, Gln, Gly) amino acid motive and ends with a SS (Ser, Ser) motive. The length of FR 4 is 11 amino acids.

The determination of the CDRs in a VL-chain on the basis of the Kabat-System is exemplified for a Vκ-region. The Vκ-region region has a typical cysteine at position 23 (Kabat position). The first amino acid of CDR 1 always starts after the cysteine (Kabat position 24). The CDR1 is typically of 10 to 17 amino acids in length and ends directly before a conserved motive like WYQQ (Trp, Tyr, Gln, Gln) (Kabat position of W: 35). FR2 has always a length of 15 amino acids and is followed by CDR 2. A typical motive of the last 4 amino acids of FR2 is LLIY (Leu, Leu, Ile, Tyr). The last amino acid of FR2 is at Kabat position 49. The length of CDR 2 is always 7 amino acids. CDR 2 is followed by FR3 that has a length of 32 amino acids in almost every case and starts typically with a motive as GVP (Gly, Val, Pro) or GIP (Gly, Val, Pro) (first amino acid of FR3 is at Kabat position 57) and ends always with a C (Cys) (last amino acid of FR3 is at Kabat position 88). The CDR 3 has normally a length of 9 to 11 amino acids. It is followed by FR4 that most often starts with F (Phe) (Kabat position 98) and is followed by a GGG (Gly, Gly, Gly), GAG (Gly, Ala, Gly), GPG (Gly, Pro, Gly) or GQG (Gly, Gln, Gly) amino acid motive and ends with motive similar or identical to KLEIK (Lys, Leu, Glu, Ile, Lys) or KVEIK (Lys, Val, Glu, Ile, Lys). The length of FR 4 is 10 amino acids.

When following the above described rules, a person of ordinary skills in the art was easily in the position to identify the following CDRs in the sequences provided in the application.

CDR-Definitions in the US application 09/554,465

Seq-ID	61	63	65
Figure No	6.3	6.4	6.5
Seq-Name	3-1	3-5	3-8
CDR H1	NYWLG	SYGLS	NYWLG
CDR H2	DLFPGSGNTHYNERFRG	EVYPRIGNAYYNEKFKG	DIYPGSGNTHYNERFRG
CDR H3	LRNWDEAMDY	RGSYGSNYDWYFDV	LRNWDEPMDY
CDR L1	RASKSISKYLA	RSSQSLVHSNGNTYLH	RASKSISKYLA
CDR L2	SGSTLQS	KVSNRFS	SGSTLQS
CDR L3	QQHNEYPYT	SQSTHVPYT	QQHNEYPYT

Seq-ID	67	69	71
Figure No	6.6	6.7	6.8
Seq-Name	4-1	4-4	4-7
CDR H1	NYWLG	NYWLG	NYGLS
CDR H2	DIFPGSGNAHYNEKFKG	DIYPGSGNTHYNERFRG	EVYPRIGNAYYNEKFKG
CDR H3	LRNWDEAMDY	LRNWDEAMDY	RGSYDTNYDWYFDV
CDR L1	KSSQSLLNSGNQKNYLA	RASKSISKYLA	RSSQSLVHSNGNTYLH
CDR L2	GASTRES	SGSTLQS	KVSNRFS
CDR L3	QNDYSYPYT	QQHNEYPYT	SQSTHVPYT

Seq-ID	73	75	77
Figure No	6.9	6.10	7
Seq-Name	5-3	5-10	5-13
CDR H1	RYWMS	NYWLG	NYWLG
CDR H2	EINPDSSTINYTPSLKD	DIFPGSGNIHYNEKFKG	DIFPGSGNAHYNEKFKG
CDR H3	GAFLFDY	LRNWDEPMDY	LRNWDEAMDY
CDR L1	SASSSISSNYLH	KSSQSLLNSGNQKNYLT	KSSQSLLNSSNQKNYLA
CDR L2	RTSNLAS	WASTRES	GASIRES
CDR L3	QQGSSIPLT	QNDYSYPLT	QQYYSYPYT

With the knowledge of the CDRs of the VH and the VL domains described in the US application No 09/554,465 **and** the general knowledge with regard to the technology described e.g. in the US Patent 5,225,539 the person skilled in the art was in the position

to provide an epitope binding domain or a recombinant polypeptide identified by the method according to the '465 application.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: October 10, 2006

Dr. Tobias Raum

Enclosures: As stated above

Curriculum vitae

Personal Data:

Name, First names:	Raum, Tobias Johannes
Date and place of birth:	September 8, 1967, in Munich, Germany
Nationality:	German
Address:	Pienzenauerstr. 110, 81825 Munich, Germany

Education:

Sept. 1973-July 1977:	Elementary school in Eurasburg/Beuerberg, Germany.
Sept. 1977-July 1986:	High school Geretsried, Germany.

University:

Oct. 1988-June 1994:	Diploma studies Biology (University of Bayreuth, Germany). Specialization in Microbiology, Genetics. Diploma thesis (July 1993-May 1994) Title: Genetic characterization of the obligately chemolithotrophic Nitrogen-fixating *Streptomyces thermoautotrophicus*. Final Degree: Diploma June 1994
Nov. 1994-Dec. 1998:	Ph.D. thesis (Institute for Immunology, Prof. G. Riethmüller, Ludwig-Maximilians-University, Munich). Topic: Generation and characterization of fully human anti-EpCAM antibodies for the therapy of epithelial tumors in the stage of minimal residual disease.

Internships:

Sept. 1990-Nov. 1990:	Trainee (Department for Genetics, Prof. L. Rothman-Denes, University of Chicago, USA). Title: Genetic engineering of the phage N4.
June 1992-Sept. 1992:	Trainee (Department for Microbial Physiology, Prof. N. Tandeau de Marsac, Institut Pasteur, Paris, France. Topic: Studies of the taxonomic classification of the four HTF *Mastigocladus laminosus* strains PCC7517, PCC 7518, PCC 7519 and PCC7702.

Curriculum vitae

Career:

July 2001-now:	Group leader Lead Discovery at the Micromet AG, Munich, Germany. From Sept. 2002 Head of Lead Discovery, from Mai 2004 Director Lead Discovery. Development of immunetherapeutics, generation of suitable antibody based human and non-human antibody specificities via phage display and conventional hybridoma technology, optimization, humanization of such specificities, determination of target epitopes.
Jan. 1999-Mai 2001:	Group Leader Molecular Design at the Connex GmbH, Martinsried, Germany. From Jan. 2001 Projektleader Bispecific immuntherapeutics recruiting human effector cells via the zeta-chain. Development of human immuntherapeutics on the basis of antibody fragments, generation of such antibody specificities via phage display technology or conventional hybridoma technology and other projects with different topics in the field of immunology and molecular biology.

Additional qualifications:

Languages:	English and French fluently.

Publications:

Oberneder R, Weckermann D, Ebner B, Quadt C, Kirchinger P, **Raum T**, Locher M, Prang N, Baeuerle PA, Leo E.
A phase I study with adecatumumab, a human antibody directed against epithelial cell adhesion molecule, in hormone refractory prostate cancer patients.
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Maletz K, Kufer P, Mack M, **Raum T**, Pantel K, Riethmuller G, Gruber R.
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Int J Cancer. 2001 Aug 1;93(3):409-16.

Raum T, Gruber R, Riethmuller G, Kufer P.
Anti-self antibodies selected from a human IgD heavy chain repertoire: a novel approach to generate therapeutic human antibodies against tumor-associated differentiation antigens.
Cancer Immunol Immunother. 2001 May;50(3):141-50.